and eGFR between 30 and 75 ml/min/1.73 m2, were enrolled in 2 parallel, multinational, double-blind, randomized, placebo-controlled studies. Subjects were randomized to atrasentan 0.75, 1.25 mg QD or placebo for 12 wks after a run-in period that maximized the RASi dose. Results: Mean UACR values (placebo, 0.75, 1.25 mg) at baseline: 671, 878, and 826 mg/g; wk 2: 696 (NS), 573 and 515 mg/g, ($p < 0.001$); and wk 12: 797 (NS), 521 and 470 mg/g ($p < 0.001$). More than 30% albuminuria reduction was observed in 51 and 55% of subjects receiving atrasentan. eGFR (49 ± 13, 48 ± 15, and 51 ± 14 ml/min at baseline) did not change significantly compared with placebo. Mean LDL-C changed by $+2 \pm 3$, -13 ± 2 and -13 ± 2 mg/dl ($p < 0.001$). Similar changes were observed in triglyceride levels. No differences were noted in the rate of peripheral edema or heart failure. At week 2, body weight increased (0.7 and 1.2 kg), but weight was not significantly different from baseline at week 12 for the 0.75 mg group. After stopping atrasentan for 30 days, all of the parameters described above returned to pretreatment values. Conclusions: Chronic administration of atrasentan reduces albuminuria in patients who are receiving maximum RAS inhibition without incurring volume-related adverse events.

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A placebo-controlled study of ambrisentan in subjects with idiopathic pulmonary fibrosis (ARTEMIS-IPF)

Hunter Gillies[a], N. Henig[a], P. Pederson[b], L. Shao[a], J. Chien[b], T. O'Riordan[b], ARTEMIS IPF Investigators

[a]*Gilead Sciences Inc., Foster City, CA, USA*
[b]*Gilead Sciences, Inc., Seattle, WA USA*
E-mail address: Hunter.Gillies@gilead.com (H. Gillies)

Rationale: Idiopathic pulmonary fibrosis (IPF) is characterized by the formation and proliferation of fibroblast foci. Endothelin-1 induces lung fibroblast proliferation and contractile activity via the endothelin A (ETA) receptor. Data from preclinical models suggests that endothelin blockade can attenuate pulmonary fibrosis. This study tested the hypothesis that ambrisentan, an endothelin type A receptor specific antagonist approved for the treatment of pulmonary arterial hypertension, reduces disease progression in subjects with idiopathic pulmonary fibrosis (IPF). Methods: This was a randomized (2:1), double-blind, placebo-controlled, event-driven trial enrolling subjects with IPF. Randomization was stratified by the presence of pulmonary hypertension at baseline, determined by a right heart catheterization, and IPF diagnosis by surgical lung biopsy. The primary endpoint was time to IPF disease progression, defined as all-cause mortality, adjudicated respiratory hospitalization, or a categorical decrease in lung function defined as a 10% decrease in forced vital capacity [FVC] with a 5% decrease in the diffusion capacity for carbon monoxide [DLCO] or a 15 % decrease in DLCO with a 5% decrease in FVC. Results: At 75% (492 subjects) of the intended total enrolment and after a mean exposure of 34 weeks to the study drug, the Data Safety Monitoring Board terminated the study due to a low likelihood of demonstrating efficacy. From 136 clinical sites, 329 and 163 subjects were randomized to receive ambrisentan or placebo respectively. At baseline, 36 (11%) and 18 (11%) subjects had pulmonary hypertension (PH) with a mPAP > 25 mm Hg and wedge pressure < 15 mm Hg in the ambrisentan and placebo groups respectively. Ambrisentan treated subjects had more primary endpoint events (90 [27.4%] versus 28 [17.2%]), and a 1.74 fold increase in risk of meeting the primary endpoint (95% confidence interval [CI] 1.14–2.66, $p = 0.010$). Evaluation of the primary endpoint components indicated that the number of deaths (hazard ratio [HR] 2.08, 95% CI 0.75–5.76, $p = 0.100$) and subjects with a categorical decrease in lung function (HR 1.53, 95% CI 0.84–2.78, $p = 0.109$) was not statistically significantly different between the groups. However, ambrisentan treated subjects had more respiratory hospitalizations (44 [13%] versus 9 [6%]), and a 2.59 fold increase in risk of experiencing a respiratory hospitalization (95% CI 1.14–5.89, $p = 0.007$). Stepwise Cox multivariate analysis revealed that after adjustment for baseline IPF severity, the risk for primary events was reduced and the p-value was >0.1 (HR 1.42, 95% CI 0.85–2.05, $p = 0.108$). Although the risk for respiratory hospitalization was also reduced, the p-value remained <0.05 (HR 2.11, 95% CI 1.03–4.33, $p = 0.042$). The presence of PH at baseline did not affect these point estimates significantly. The secondary endpoints (FVC, DLCO, 6MWD, TDI and QoL) at 48 weeks and the incidence of liver toxicity were not statistically significantly different between the groups. Conclusions: Ambrisentan was ineffective in reducing disease progression in IPF and was associated with an increased risk of respiratory hospitalizations. While there is no evidence of treatment benefit, all analyses need to be interpreted cautiously as ARTEMIS-IPF was terminated early for lack of efficacy.

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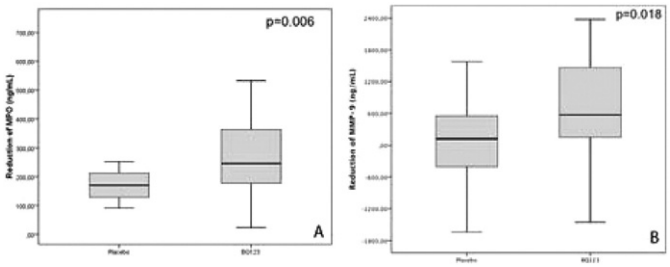
Impact of short term endothelin A receptor blockade on plasma markers for remodeling and neutrophil activation in patients with ST elevation acute coronary syndrome

Raphael Wurm[a], Christopher Adlbrecht[a], Martin Andreas[b], Bassam Redwan[a], Klaus Distelmaier[a], Guenter Klappacher[a], Irene M. Lang[a]

[a]*Medical University of Vienna, Department of Internal Medicine II, Division of Cardiology, Austria*
[b]*Medical University of Vienna, Department of Cardiac Surgery, Austria*
E-mail address: raphael.wurm@meduniwien.ac.at (R. Wurm)

Background: Endothelin (ET) is a pro-fibrotic vasoconstrictor and a mediator of microvascular dysfunction and cardiac remodeling. Animal studies investigating ET receptor blockade in acute myocardial infarction led to conflicting results regarding ventricular remodeling. In-vitro, ET-A receptor blockade decreases neutrophil activation. Methods: Patients with posterior-wall STE-ACS were treated with BQ-123, a selective ET-A receptor antagonist as previously described ($n = 54$). Peripheral blood samples were drawn at baseline, 24 h and 30 days after PCI. Myeloperoxidase (MPO), matrix metalloproteinase 9 (MMP-9) and the procollagen III N-terminal propeptide (PIIINP), were measured in plasma using commercially available assays. Results: Patients randomized to BQ-123 demonstrated a greater reduction of MPO levels from baseline to 24 h compared to placebo-treated patients ((177 ng/mL reduction for BQ-123 versus 108 ng/mL for placebo, $p = 0.006$), Fig. 1a). In addition, we observed a significantly greater reduction of MMP-9 levels in patients treated with study drug (568 ng/mL versus 117 ng/mL, $p = 0.018$, Fig. 1b).There was no significant difference in PIIINP values. Conclusion: Short-term administration of BQ-123 reduces MPO and MMP-9 plasma levels in patients with STE-ACS. In trials with larger patient numbers this may translate into improved ventricular remodeling at six months.



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